Tuning radical interactions in trisradical tricationic complexes by varying host-cavity sizes†

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Although host–guest pairing interactions between bisradical dicationic cyclobis(paraquat-p-phenylene) (BB2+) and the bipyridinium radical cation (BIPY+) have been studied extensively, host molecules other than BB2+ are few and far between. Herein, four bisradical dicaticionic cyclophanes with tunable cavity sizes are investigated as new bisradical dicaticionic hosts for accommodating the methyl viologen radical cation (MV+) to form trisradical tricationic complexes. The structure–property relationships between cavity sizes and binding affinities have been established by comprehensive solution and solid-state characterizations as well as DFT calculations. The association constants of the four new trisradical tricationic complexes are found to range between 7400 and 170 000 M⁻¹, with the strongest one being 4.3 times higher than that for [MV·BB]3+. The facile accessibility and tunable stability of these new trisradical tricationic complexes make them attractive redox-controlled recognition motifs for further use in supramolecular chemistry and mechanostereochemistry.

**Introduction**

Among the various noncovalent bonding interactions, which have been explored in the context of supramolecular chemistry, radical–radical interactions between conjugated radical cations and/or anions are relatively new on the chemical scene. The bipyridinium radical cation (BIPY+) is a well-known thermally stable species with a strong tendency to undergo π-π-dimerization (pimerization) in aqueous or confined media. The dimerization constant, however, is usually relatively low in organic solvents, a property which limits applications in supramolecular chemistry.

Cyclobis(paraquat-p-phenylene) (CBPQT4+), also known as the blue-box (BB4+), in which two BIPY2+ units are connected by two p-xylene spacers to produce a rigid, box-like conformation with a centroid-to-centroid distance of ca. 6.9 Å between two BIPY2+ units, is an excellent host for accommodating BIPY+ in its reduced state to form a trisradical tricationic complex, [BIPY·BB]3+. This complex enjoys enhanced stability on account of the macrocyclic effect, rendering the radical host–guest recognition motif attractive for templating the formation of mechanically interlocked molecules (MIMs) which otherwise cannot be made. A striking feature of this radical host–guest complex is that it can be switched (Scheme 1).

![Scheme 1](image-url)

Scheme 1. (a) Graphical representations of redox-controlled attraction and repulsion between the bisradical dicaticionic cyclopane and BIPY+. (b) Structural formulas of the range of tetracationic cyclophanes.
from radically based attraction to coulombic repulsion by oxidizing the BIPY$^{+}$ units back to their dicaticonic states, and so providing a large driving force for the relative motions of component parts inside MMs. If the coulombic repulsion-induced motions are restricted by the formation of mechanical bonds, BIPY$^{+}$ radicals with extraordinary stability can be produced, affording a new strategy for the design of persistent organic radicals.

Despite the attractive properties and applications of trisradical tricationic complexes, most of the current studies have focused on [BIPY⊂BB]$^{3+}$, and host molecules other than BB$^{2+}$ have been little investigated. We have a particular interest in developing new BB$^{2+}$ analogues with smaller cavity sizes, since the decreased separation distance between the two bipyridinium units in cyclophanes is expected to result in increased coulombic repulsion between the guest and different hosts in their oxidized states, which will be beneficial for both the operation of redox-driven molecular machines, such as molecular pumps, and the production of mechanically protected persistent organic radicals. In addition, we have observed that the centroid-to-centroid distance between two BIPY$^{+}$ units in free BB$^{2+}$ (6.9 Å) is ca. 0.5 Å larger than that (6.4 Å) present in [BIPY$^{−}$⊂BB]$^{3+}$, indicating that a cavity size slightly smaller than that present in BB$^{3+}$ could be even more favourable for the formation of highly stable trisradical tricationic complexes.

Herein, we describe the syntheses of four tetracationic cyclophanes (Scheme 1b), one (mpBB$^{2+}$) with m- and p-xylene linkers and three (PyBB$^{2+}$, DThBB$^{2+}$ and ThBB$^{2+}$) with either 2,6-pyridinedimethyl or 2,5-thiophenedimethyl linkers, which retain similar rigidities and conformations to BB$^{2+}$, while the separation distances between the two BIPY units are gradually decreased (Scheme 1b). Complexation of the methyl viologen radical cation (MV$^{+}$) with these four cyclophanes—mpBB$^{2+}$, PyBB$^{2+}$, DThBB$^{2+}$ and ThBB$^{2+}$—in their reduced states afforded four new trisradical tricationic complexes—[MV⊂mpBB]$^{3+}$, [MV⊂PyBB]$^{3+}$, [MV⊂DThBB]$^{3+}$ and [MV⊂ThBB]$^{3+}$—that were characterised fully by UV-vis-NIR spectroscopy, cyclic voltammetry (CV), and X-ray crystallography. We have discovered that the sizes of the cyclophane cavities exert a large influence on the magnitude of the association constants in MeCN between these four reduced cyclophanes and MV$^{++}$.

Results and discussion

All four tetracationic cyclophanes, namely, mpBB$^{2+}$, PyBB$^{2+}$, DThBB$^{2+}$ and ThBB$^{2+}$, were prepared—see ESI†—by exploiting the tetrabutylammonium iodide (TBAI) catalysed cyclisation, which involves the reaction of the bis(pyridinium) salt precursor (HS-2PF$_6$) with 1,4-bis(bromomethyl)benzene or 2,5-bis(bromomethyl)thiophene in the presence of 20 mol% TBAI in MeCN while stirring under reflux for 4 days. The products were purified by exploiting normal-phase silica gel column chromatography and were obtained in isolated yields (28–52%) which were higher than that (19%) obtained for BB$^{4+}$ under identical conditions, probably because of the decreased ring strain in the four cyclophanes.

The electrochemical properties of these four cyclophanes, as their 4PF$_6$ salts, were investigated by cyclic voltammetry (CV) in MeCN at room temperature. The CV curves of these four cyclophanes plus that of BB-4PF$_6$ showed (Fig. S7†) two reversible reduction waves which are characteristic of BIPY$^{2+}$ units. The positions of the two reduction waves for the four new cyclophanes are similar to those observed for BB-4PF$_6$, with only slight shifts of no more than 0.12 V compared with BB-4PF$_6$. These observations are in accordance with our expectations, since the linkers in these cyclophanes should have no significant influence on the electrochemical properties of their BIPY$^{2+}$ units.

The formation of the four new trisradical tricationic complexes were investigated by UV-vis-NIR spectroscopy. Methyl viologen (MV$^{2+}$) was chosen as the representative guest for studying host-guest complexation. The tetracationic cyclophanes and MV$^{2+}$ were reduced separately in MeCN using Zn dust to yield suspensions which were filtered to remove the reducing agent. The resulting blue solutions displayed (Fig. 1) similar strong absorptions characteristic of BIPY$^{+}$ units in the range 500–700 nm. When the bisradical dicaticonic cyclophanes were mixed with 1 equiv. MV$^{++}$, new broad peaks appeared at around ca. 1100 nm, characteristic of trisradical tricationic complexes. Hence, despite the different constitutions of the linkers, all four cyclophanes retained their ability to host MV$^{++}$ in their reduced states. The association constants ($K_a$) for the trisradical tricationic complexes were obtained (Fig. 1) by UV-vis-NIR titrations. The absorption changes at ca. 1100 nm were monitored and matched to 1 : 1 isotherms to give the binding constants (Table 1) for all four complexes. In addition, the $K_a$ value for [MV⊂BB]$^{3+}$ was found, in a control experiment (Fig. S2†), to be $(3.9 ± 0.5) \times 10^4$ M$^{-1}$ in agreement with the previously reported $K_a$ value. For mpBB$^{3+}$ and PyBB$^{3+}$, which have very similar constitutions and cavity sizes, $K_a$ values of $(8.9 ± 1.3) \times 10^3$ M$^{-1}$ and $(7.4 ± 0.6) \times 10^3$ M$^{-1}$ were obtained, respectively. Notably, both the two thiophene-
containing compounds DThBB\(^{3(+)}\) and ThBB\(^{3(+)}\) display much stronger binding affinities than mpBB\(^{2(+)}\) or PyBB\(^{3(+)}\), with their respective \(K_a\) values of \((6.7 \pm 3.8) \times 10^9\) M\(^{-1}\) and \((1.7 \pm 0.6) \times 10^8\) M\(^{-1}\), which are also higher than that \((K_a = 3.9 \pm 0.5) \times 10^8\) M\(^{-1}\) of BB\(^{2(+)\text{aff}}\). These results demonstrate the all-important influence of the linkers on the association constants of these four new trisradical tricationic complexes.

In order to gain a better understanding of the reasons behind the different binding strengths of the dicaticonic diradical cyclophanes towards MV\(^{+}\), single crystals of the four trisradical tricationic complexes were grown by vapor diffusion of iPr\(_2\)O into equimolar solutions in MeCN of the corresponding method calculated binding energies of the trisradical triscationic complexes.

<table>
<thead>
<tr>
<th></th>
<th>(d_1^a) Å</th>
<th>(d_2^b) Å</th>
<th>(K_a^c) M(^{-1})</th>
<th>(E_{\text{Exp}}^d) kJ mol(^{-1})</th>
<th>(d_{\text{Calc}}^e) Å</th>
<th>(E_{\text{Calc}}^f) kJ mol(^{-1})</th>
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<td>6.90</td>
<td>39 000 \pm 5000</td>
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<td>6.71</td>
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<tr>
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<td>6.56</td>
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<tr>
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<td>8900 \pm 1300</td>
<td>-22.5</td>
<td>5.73</td>
<td>-95.1</td>
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<tr>
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<td>5.65</td>
<td>—</td>
<td>7400 \pm 600</td>
<td>-22.1</td>
<td>5.50</td>
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\(^a\) Centroid-to-centroid distances of BIPY\(^{2(+)\text{aff}}\) units in tetracationic cyclophanes according to solid-state structures. \(^b\) Centroid-to-centroid distances of BIPY\(^{3(+)\text{aff}}\) units in bisradical dicaticonic cyclophanes according to solid-state structures. \(^c\) Binding constants of the trisradical triscationic complexes from vis/NIR titrations. \(^d\) Binding energies of the trisradical triscationic complexes calculated from vis/NIR titrations. \(^e\) Centroid-to-centroid distances of BIPY\(^{3(+)\text{aff}}\) units in bisradical dicaticonic cyclophanes according to B3LYP-D3-optimized structures solvated in acetonitrile. \(^f\) B3LYP-D3 method calculated binding energies of the trisradical triscationic complexes.

and the MV\(^{+}\) axis of around 75°. Although the cavity sizes for the individual bisradical dicaticonic cyclophanes are quite different (Table 1) from each other, the distances between the two BIPY\(^{3(+)\text{aff}}\) units in the trisradical triscationic complexes are almost the same, with MV\(^{+}/\text{BIPY}^{3(+)\text{aff}}\) contact distances (Fig. 2) of 3.16–3.19 Å and the centroid-to-centroid distance of two cyclophane BIPY\(^{3(+)\text{aff}}\) units of around 6.3 Å. This phenomenon is an example of “induced-fit” binding—i.e., the cyclophanes adjust their conformations (extend or shrink the cavity sizes) to best accommodate MV\(^{+}\) guests and thus optimise the radical-pairing recognition interactions. Accordingly, we assumed that the ideal cavity size for accommodating MV\(^{+}\) guests is around 6.3 Å, with smaller or larger sizes resulting in decreased binding affinities towards MV\(^{+}\).

Subsequently, we analysed the crystal structures of the individual cyclophanes in both their oxidised and reduced forms. All four tetracationic cyclophanes readily formed good crystals which were suitable for X-ray crystallographic analyses. The centroid-to-centroid distance (Fig. 3c) between the two BIPY\(^{2(+)\text{aff}}\) units of the symmetric tetracationic DThBB\(^{4(+)}\) is 5.80 Å, which is ca. 0.5 Å smaller than the “ideal size” of 6.3 Å for binding MV\(^{+}\) by the bisradical dicaticonic cyclophanes. PyBB\(^{4(+)}\) featured (Fig. 3b) a trapezoid-like conformation in view of the different separation distances for the p-xylene and 2,6-pyridinedimethyl linkers. Consequently, the distance between the two BIPY\(^{2(+)\text{aff}}\) units gradually decreases upon going from the p-xylene linker to the m-xylene linker, and the centroid-to-centroid distance (Fig. 4b) of the two BIPY\(^{2(+)\text{aff}}\) units is ca. 5.65 Å (Fig. 4), which is about 0.65 Å smaller than 6.3 Å.
The crystal structures (Fig. 3a and d, S8, and S10†) of the other two asymmetric cyclophanes, mpBB+i and ThBB+i, exhibit disorder in the m-xylylene/p-xylylene or p-xylylene/2,5-thiophenedimethyl linkers. Consequently, both mpBB+i and ThBB+i display a symmetric conformation according to X-ray crystallographic analysis with an apparent centroid-to-centroid distance between BIPY2+ units of 5.94 and 6.10 Å, respectively. Since mpBB+i has an almost identical constitution to that of PyBB+i, the actual conformations and cavity sizes of these two cyclophanes should be similar to each other. Therefore, the apparent centroid-to-centroid distances in mpBB+i (5.94 Å) and ThBB+i (6.10 Å), which were deduced from the crystal structures, may not be all that accurate as a consequence of the disorder. In general, these solid-state structures, however, do provide some clues when it comes to interpreting the trend in the host–guest association constants obtained from titration experiments in their reduced states. Since the cavity sizes of DThBB+i (5.8 Å) and BB+i (6.8 Å) are either ca. 0.5 Å smaller or larger than 6.3 Å, their binding constants when reduced to bisradical dications for hosting MV+i are quite similar, i.e., (6.7 ± 3.8) × 10^4 vs. (3.9 ± 0.5) × 10^6 M⁻¹. The asymmetric ThBB+i, which can be regarded as an “averaged” version of DThBB+i and BB+i, displays a binding constant (1.7 ± 0.6) × 10^6 M⁻¹ for [MV ⊂ ThBB+i]^0(+) that is higher than those for both [MV ⊂ DThBB+i]^0(+) and [MV ⊂ BB+i]^0(+) The other two cyclophanes, PyBB+i and mpBB+i, which have asymmetric constitutions and much smaller cavities, display much lower binding constants (7.4 ± 0.6) × 10^5 M⁻¹ and (8.9 ± 1.3) × 10^5 M⁻¹, respectively) for [MV ⊂ PyBB+i]^0(+) and [MV ⊂ mpBB+i]^0(+) When the cavity size is decreased even further, as in the case of mBB+i (5.26 Å) with its two m-xylylene spacers (Scheme 1), no binding towards MV+i in its reduced state was observed either in solution or in the solid state.

We also obtained the crystal structures of the bisradical dicaticonic forms of the cyclophanes, DThBB+i, ThBB+i, and mpBB+i, while PyBB+i failed to form single crystals suitable enough for X-ray crystallography. Again, disorder also plagued (Fig. 4b and S13†) the crystal structure of ThBB+i on account of its having two different linkers. No disorder, however, was observed in the case of the other asymmetric cyclophane mpBB+i. Notably, all three bisradical dicaticonic cyclophanes formed (Fig. 4, S11–S13†) one-dimensional stacked columns in the solid state on account of intermolecular radical–radical interactions between adjacent BIPY+i units, in a manner similar to that already reported for BB+i, with distances (Fig. 4) between stacked BIPY+i units in neighbouring bisradical dicaticonic cyclophanes of 3.36, 3.09 and 3.11 Å for mpBB+i, DThBB+i and ThBB+i, respectively. Consequently, these bisradical dicaticonic cyclophanes display significantly longer centroid-to-centroid BIPY+i distances than the corresponding BIPY+i distances (Fig. 3 and Table 1) in the tetracationic cyclophanes in their solid states, most likely as a result of the strong intermolecular radical–radical interactions enlarging the cavities of the bisradical dicaticonic cyclophanes in the solid states. In solution, however, the intermolecular stacking interactions between bisradical dicaticonic cyclophanes will be negligible, and the solution-phase cavity sizes are expected to be smaller than those observed in their solid states.

Finally, density functional theory (DFT) calculations using B3LYP basis set with D3 dispersion correction were performed in order to investigate the binding energies of the trisradical tricationic complexes. The optimised structures of the bisradical dicaticionic hosts were optimised (Fig. S18†) showing that the predicted cavity sizes—centroid-to-centroid distances between BIPY+i units—are in better agreement (Table 1) with the measured distances in the tetracationic cyclophanes in the solid state than those of the bisradical dicaticonic cyclophanes. The calculations predict (Table 1 and Fig. 5b) the host–guest binding energies to be in the order of |ΔE_FHBB+i| < |ΔE_BB+i| < |ΔE_FFHBB+i| < |ΔE_mpBB+i| < |ΔE_PYBB+i| in agreement with the experimental results. The binding energies with MV+i exhibit strong dependences on

Fig. 4. Solid-state structures of (a) mpBB+i, (b) DThBB+i; (c) ThBB+i. Left: plan views depicted as tubular representations; right: 1D packing of the diradical dicaticonic cyclophanes depicted as tubular superimposed upon space-filling representations. Hydrogen atoms and disorder in the asymmetric cyclophanes are omitted for the sake of clarity.
the cyclophane cavity sizes. In an attempt to analyse the correlations between the cavity sizes and the binding energies, we decomposed (Table S2†) the binding energies into the contributions from dispersion and electrostatic energies. The attractive dispersion interactions (Table S2†) weaken with increasing host size, while the concomitant decrease (Table S2†) in electrostatic repulsion stabilises host-guest binding. Thus, it is the competition between the two counter-acting interactions which results in the optimal host-guest binding (Fig. 5) at a cavity size of ca. 6.3 Å, i.e., as exemplified by ThBB2(+)†.

Conclusions

Four bisradial dicaticonic cyclophanes were investigated as hosts for binding MV+ and found to form trisradical trisca-tionic complexes. UV-vis-NIR titration experiments, X-ray crystallographic characterizations and DFT calculations revealed that the binding affinities of these trisradical triscationic complexes are highly dependent on the cavity sizes of the bisradical dicaticionic cyclophanes. The structure-property relationship we have established will provide useful information for the design of new radical hosts-guest pairs in the future. Notably, the asymmetric p-xylene/2,5-thiophene-dimethyl linked cyclophane ThBB2(+)† which displayed an association constant of 170 000 M−1 in acetonitrile, that is 4.3 times higher than that (39 000 M−1) of BB2(+) which has two p-xylene linkers. The facile accessibility, tunable association constants, as well as decreased host cavity sizes associated with these four new trisradical tricaticionic complexes, make them attractive redox-controlled recognition motifs for further use in supramolecular chemistry and in the template-directed synthesis of mechanically interconnected molecules.

Conflicts of interest

There are no conflicts to declare.

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Notes and references


14 A bolded descriptor denotes a compound, be it free or complexed, and an unbolded descriptor refers to either (i) a component within a molecule or (ii) a component part of a mechanically interlocked molecule.